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(54) Title: LIQUID CALCIUM SUPPLEMENTATION FROM READILY SOLUBLE MIXTURES OF CALCIUM COMPOUND AND CITRIC ACID

(57) Abstract

A composition of matter consisting essentially of citric acid and one or more calcium compounds selected from the group consisting of calcium hydroxide, calcium carbonate and calcium oxide. The composition of matter is preferably a substantially dry mixture which may be used, for example, as a powder for making an 'instant' beverage of potable liquid. A preferred calcium compound/citric acid molar ratio in the composition of matter of the present invention is between about 0.6 and about 1.5. In a most preferred embodiment, the composition of matter of the present invention consists essentially of calcium hydroxide and citric acid having a calcium compound/citric acid or calcium hydroxide/citric acid molar ratio of about 1.25. The composition of matter of the present invention has a utility demonstrated by dissolution in water to form a liquid dietary calcium supplement comprising soluble calcium citrate. This composition of matter may comprise one or more of a flavorant, lubricant, sweetener or colorant usable to maintain a powdery texture or to enhance the flavor of a beverage prepared therefrom.

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LIQUID CALCIUM SUPPLEMENTATION FROM READILY SOLUBLE
MIXTURES OF CALCIUM COMPOUND AND CITRIC ACID

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This application is a continuation-in-part of co-pending applications serial numbers 703,196 filed February 19, 1985; 807,530 filed December 11, 1986; serial number 840,884 filed March 18, 1986; International application number PCT/US86/00314, filed February 19, 1986; and serial number 896,651 filed August 13, 1986.

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The mineral calcium is an important human dietary component. Calcium is required for adequate bone formation and maintenance, as well as for diverse metabolic functions. These diverse metabolic functions of calcium are incompletely understood but likely to involve, at least in part, the alteration and functional control of proteins such as enzymes.

An assurance of adequate dietary calcium intake is thus important for normal development, metabolism and maintenance. Dietary calcium intake alone however is insufficient to assure that adequate calcium levels are 5 available for required body functions. Dietary calcium must be absorbed from the digestive tract before it may be utilized. Furthermore, the urinary excretion of absorbed calcium must be considered, particularly for individuals who may be subject to the formation of calcium-containing 10 kidney stones.

The intestinal absorption of calcium is enhanced by vitamin D and may also be affected by the particular chemical form of ingested calcium.

15 Among the conditions of particular relevance to calcium dietary requirements is osteoporosis. Osteoporosis, a condition characterized by decreases in bone mass, renders bones more fragile and susceptible to fracture. The 20 increasingly older population of this country, since osteoporosis is usually an age-related phenomenon, further accentuates the significance of this condition. Postmenopausal women are generally agreed to be most susceptible to osteoporosis. As demonstrated by Heaney et al., 25 (J. Lab. Clin. Med. (1978) Vol. 92 No. 6 pp. 953 to 963), postmenopausal women, unless treated with estrogens, required an increased calcium intake to maintain a zero calcium balance. This increased required intake was ascribed as due to a decrease in the production of an 30 active vitamin D compound and calcium absorption, both perhaps related to the absence of estrogens. Recker et al., (Annals Int. Med. (1977) Vol. 87 No. 6 pp. 649 to 655) demonstrated that further bone losses in osteoporosis prone postmenopausal women may be prevented by estrogen

treatment or, to a lesser extent, by dietary calcium carbonate supplementation.

5 In an additional study concerning osteoporosis of postmenopausal women, Nordin et al., (Brit. Med. J. (1980) Vol. 280 pp. 451 to 454) found three treatments that succeeded in lessening or abolishing further bone deterioration. These three treatments were: dietary calcium supplementation; estrogenic hormone treatment; and, treatment 10 with estrogenic hormone plus 1 alpha hydroxy vitamin D₃.

Treatment of individuals with estrogenic hormones may have adverse effects, such as the stimulation of estrogen-dependent tumors. Treatment of individuals with vitamin D derivatives may be inadvisable because of potentially toxic effects when excess vitamin D is administered. An effective dietary calcium supplementation appears to be an 15 advisable treatment for osteoporosis.

20 In certain individuals however, dietary calcium supplementation may increase urinary calcium and lead to formation of calcium-containing kidney stones (nephrolithiasis).

25 Kidney stone formation may result from a number of conditions, one of which is the presence of undue amounts of calcium in urine. Pak et al., (N. Eng. J. Med. (1974) Vol. 290 pp. 175 to 180) have shown that urinary calcium levels and renal calcium stone formation are decreased 30 when patients with a history of recurrent calcium nephrolithiasis are fed low calcium diets and treated orally with cellulose phosphate. Pak (Urolithiasis Research (1976) ed. by H. Fleisch et al., Plenum Pub. Co., N.Y., N.Y. pp. 213 to 224) demonstrated that when patients with 35 absorptive hypercalciuria are fed calcium gluconate, they

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exhibited increased urinary calcium, leading to an increased activity product ratio, a measure of the degree of urinary calcium oxalate saturation. Thus, calcium supplementation made them more prone to form kidney 5 stones, since their urine became more supersaturated with respect to a common stone salt (calcium oxalate).

Belizan et al., (J. Am. Med. Ass'n. (1983) Vol. 249 No. 9 pp. 1161 to 1165) indicated that young adults showed 10 reduction in blood pressure when their diets were supplemented with 1 gm/day elemental calcium (calcium carbonate and calcium lactate-gluconate). A similar observation was made with pregnant women (Belizan et al., Am. J. Obstet. Gynecol (1983) Vol. 146 No. 2 pp. 175 to 180). Currently, 15 a possibility exists that adequate calcium intake may be an important factor in control of blood pressure. Additionally, it has been proposed that the incidence of colon cancer may be lessened by increases in dietary calcium intake.

20 Chronic diarrheal syndrome, where bone loss may occur, also sometimes involves calcium nephrolithiasis. This syndrome may result from surgical resection or inflammation of the digestive tract. Bone disease may 25 occur because patients with this condition absorb calcium poorly from intestines. Kidney stones may develop from different causes including concentrated urine, undue acidity of urine and low urinary citrate. While these patients require calcium supplements for prevention of 30 bone loss, they face the danger of forming more kidney stones when they take more calcium.

Supplementation of the diet with calcium appears to be an important step for control of adverse conditions 35 including osteoporosis, bone loss in chronic diarrheal

syndrome and possibly at least certain types of hypertension and colon cancer. Such calcium supplementation however, may cause undesirable effects, particularly nephrolithiasis.

5

Dietary calcium supplementation is generally agreed as most effective when the calcium is efficiently absorbed from the digestive tract. Thus a method of providing efficiently absorbed calcium while inhibiting calcium nephrolithiasis is needed.

10 nephrolithiasis is needed.

The following is a more detailed clinical description of some of above conditions, as well as a description for additional conditions, in which calcium citrate (especially in the special liquid form as embodied in this invention) may be useful.

Hypoparathyroidism. Hypoparathyroidism (either parathyroid hormone-deficient or resistant) is characterized clinically by hypocalcemia (low blood calcium from impaired skeletal mobilization and intestinal absorption of calcium) and hyperphosphatemia (high blood phosphate from defective renal phosphate clearance) (Breslau and Pak, Metabolism, Vol. 28, pp 1261-1276, 1979). It has been customary to provide calcium supplementation and exogenous vitamin D substances to correct these disturbances

While there has been considerable progress in the therapeutic management with the introduction of active vitamin D metabolite (1,25-(OH)₂vitamin D) in the marketplace, three areas continue to be of some concern. First, some patients may show variable response to 1,25-(OH)₂vitamin D and may sometimes develop hypercalcemia/hypocalcemia. Second, substantial

hypercalciuria (high urinary calcium) may ensue when normal serum calcium concentration is restored by treatment. Some patients may develop kidney stones. Third, serum phosphorus may remain high, especially when 5 vitamin D substances are given. The need for a calcium supplement, which provides available calcium as well as bind phosphate, would seem to be clear.

Postmenopausal Osteoporosis. Considerable interest 10 has been generated recently concerning potential therapeutic role of calcium supplements in the prevention of postmenopausal osteoporosis. The rationale for the use of calcium supplements in postmenopausal osteoporosis is the finding that calcium absorption is often depressed, 15 presumably because of the defective renal synthesis of $1,25-(OH)_2$ vitamin D. Thus, a higher calcium intake is needed by postmenopausal women to prevent negative calcium balance. Heaney et al., (J. Lab. Clin. Med., Vol. 92, p 953, 1978), showed that the amount of calcium intake 20 required to achieve zero calcium balance increased by approximately 500 mg/day to nearly 1500 mg/day with the onset of menopause. Their study provided experimental basis for the recommendation by the recent Consensus 25 Development Conference on Osteoporosis that calcium intake of 1000-1500 mg/day be provided in order to "reduce the incidence of osteoporosis in postmenopausal women." Since the average dietary calcium intake of postmenopausal American women is only about 500 mg/day, the need for calcium supplementation would seem to be clear.

30

End-stage Renal Disease. The pathogenetic mechanisms responsible for the development of renal osteodystrophy are multifactorial. They include renal phosphate 35 retention, intestinal malabsorption of calcium, renal aluminum retention and acidosis. There is some evidence

that these disturbances could be ameliorated by calcium citrate therapy.

Considerable evidence supports the view that 5 phosphate retention plays a major role in the development of secondary hyperparathyroidism in renal failure. Phosphate retention, resulting from a reduction in glomerular filtration rate, may cause a transient decline 10 in serum calcium concentration in mild-moderate renal disease. In an attempt to normalize serum calcium and phosphorus levels, parathyroid hormone secretion is increased, leading to secondary hyperparathyroidism. When 15 the glomerular filtration rate declines to less than 25% of normal, significant hyperphosphatemia may supervene because of inadequate compensation by parathyroid stimulation. Secondary hyperparathyroidism accounts for the development of osteitis fibrosa (bone destruction), whereas hyperphosphatemia contributes to soft tissue calcification

20 The intestinal calcium absorption is typically reduced in end stage renal disease, largely due to the defective renal synthesis of 1,25-(OH)₂vitamin D. The reduced intestinal calcium absorption contributes to the 25 development of secondary hyperparathyroidism. Exogenous 1,25-(OH)₂vitamin D may restore normal intestinal calcium absorption, but may be complicated by frequent development of hypercalcemia (high blood calcium).

30 Although aluminum metabolism in normal persons is poorly understood, previous studies have demonstrated that intestinal absorption and renal excretion normally play a key role in aluminum metabolism. Aluminum toxicity is rare in persons with normal renal function because of 35 efficient renal elimination. With the loss of renal

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function, however, aluminum accumulates in the body, especially in bone. Bone biopsy specimens from dialysis patients demonstrated a strong correlation between the presence of osteomalacia (impaired mineralization of bone) 5 and elevated levels of aluminum in bone (Hodson et al., Ann. Int. Med., Vol. 94, pp. 629-637, 1981). There is substantial experimental evidence supporting the view that aluminum accumulation in bone causes osteomalacia.

10 Initial reports of aluminum intoxication resulting in osteomalacia were in patients undergoing dialysis with dialysate prepared from tap water containing high levels of aluminum. The establishment of standards for permissible levels of aluminum in dialysate (less than 10 ug per liter) resulted in a decrease in these diseases 15 from previously epidemic proportions and it was believed that aluminum toxicity would no longer afflict patients on chronic hemodialysis. Unfortunately, this has not been the case. Phosphate binding gels, principally aluminum 20 hydroxide, have been used to prevent the hyperphosphatemia in chronic renal failure and thus preventing the secondary hyperparathyroidism. Unfortunately, evidence now suggests that the aluminum load delivered to chronic renal failure patients from aluminum-containing phosphate binders 25 results in aluminum accumulation in the body causing a vitamin D resistant osteomalacia.

Metabolic acidosis frequently complicates the course of chronic renal disease because of defective renal 30 elimination of acid. Loss of bone mass may ensue, possibly because of the need to buffer the acid load by bone mineral. It has been customary to provide soluble alkali to correct the acidosis. However, the typical 35 alkali used, citrate or bicarbonate salts of sodium and potassium, impose a load of these cations which may not be

advantageous or safe in patients with end stage renal disease.

5 Essential Hypertension. There is some evidence that dietary calcium supplements may be beneficial in essential hypertension. Diet histories have disclosed a lower calcium intake among patients with essential hypertension. Serum ionized calcium has been reported to be low in the low renin subtype. Calcium supplements have been reported 10 to reduce blood pressure in preliminary trials in control subjects, pregnant women, and patients with essential hypertension.

15 There is some evidence for the varying vasopressor effects of the different types of monovalent cation and anions. The association of dietary sodium and hypertension is long recognized. On the other hand, potassium may have a protective role on blood pressure (Iimura et al., Clin. Sci., Vol. 61, pp 77-80, 1981). 20 Recently, a hypertensive role of chloride ion has been implicated. In contrast, bicarbonate ion even when given as the sodium salt has been shown to be protective against the development of hypertension. The varying effect of anions may be explained by the retardation of calcium 25 influx by alkali.

30 The present invention comprises a composition of matter consisting essentially of citric acid and one or more calcium compounds selected from the group consisting of calcium hydroxide, calcium carbonate and calcium oxide. This composition of matter preferably comprises citric acid and one or more calcium compounds selected from the group consisting of calcium hydroxide, calcium carbonate and calcium oxide. The composition of matter is 35 preferably a substantially dry mixture which may be used,

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for example, as a powder for making an "instant" beverage of potable liquid. A preferred calcium compound/citric acid molar ratio in the composition of matter of the present invention is between about 0.6 and about 3.0. In 5 a more preferred embodiment, the composition of matter of the present invention consists essentially of a mixture of calcium hydroxide and citric acid having a calcium compound/citric acid ratio of about 1.25, most preferably, a mixture of calcium hydroxide and citric acid having a 10 calcium hydroxide/citric acid molar ratio of about 1.25.

The composition of matter of the present invention has a utility demonstrated by dissolution in water to form a liquid dietary calcium supplement comprising soluble 15 calcium citrate preferably enriched with citric acid. This composition of matter may comprise one or more of a flavorant, lubricant, sweetener or colorant usable to maintain a powdery texture or to enhance the flavor and appearance of a beverage prepared therefrom.

20

The present invention also involves a method for preparing a mixture soluble in an aqueous solvent to form a potable liquid consisting essentially of calcium citrate and citric acid. This method comprises the steps of: 25 mixing a calcium compound (preferably calcium hydroxide) and citric acid in a calcium compound/citric acid molar ratio of between about 0.6 and about 3.0, preferably between about 0.6 and about 1.5 and most preferably about 1.25.

30

This potable liquid consisting essentially of calcium citrate and citric acid may be prepared by dissolving a quantity of said above-described mixture in an amount of aqueous solvent such as tap water. Such a potable liquid 35 is suitable for the dietary supplementation of calcium

without substantial risk of calcium renal stone facilitation or enhancement. The potable liquid consists essentially of: citric acid; water; and a calcium compound selected from the group consisting of calcium hydroxide, 5 calcium oxide and calcium carbonate. The potable liquid preferably has a pH between about 2 and about 7, more preferably between about 3 and about 5. The potable liquid preferably comprises calcium compound and citric acid are in a calcium compound/citric acid molar ratio 10 between about 0.6 and about 1.5. This potable liquid preferably comprises calcium in an concentration between about 500 mg/L and about 2000 mg/L and contains calcium hydroxide as the calcium compound.

15 In an important aspect, the phosphate content of the mixture or liquid of the present invention is preferably controlled so that a phosphorous/citrate weight ratio of less than about 1.5 is maintained.

20 The present invention presents evidence that mixtures of citric acid and a calcium compound such as calcium hydroxide as a form of liquid calcium supplementation is more optimal than tricalcium dicitrate provided in a tablet form. Although calcium hydroxide is a preferred 25 calcium compound, it is understood that calcium oxide and calcium carbonate may be equally useful in the practice of the present invention.

In the original patent application number 703,196 filed February 15, 1985 it was shown that calcium citrate (tricalcium dicitrato) given orally in a solid form provides a greater calcium bioavailability (absorbability) and citraturic response (rise in urinary citrate) than calcium carbonate. Thus, more calcium was absorbable from calcium citrate than from a comparable amount of calcium

carbonate (Nicar and Pak, J. Clin. Endo. Metab. Vol. 61, pp 391-393, 1985). Urinary citrate rose significantly during calcium citrate treatment, but not during calcium carbonate therapy (Harvey, Zobitz and Pak, J. Clin. Endo. Metab. Vol. 61, pp 1223-1225, 1985). Since citrate is an inhibitor of calcium (kidney) stone formation, results suggested that calcium citrate treatment would be less likely than calcium carbonate to cause such stones.

10 Subsequent related patent applications (807,530; 840,884 and 896,651), involved improved formulations of calcium citrate which possessed even greater bioavailability and citraturic effect than the original product (a solid preparation of tricalcium dicitrate).
15 Since the solid form of calcium citrate must be dissolved in the intestinal tract before it is absorbed or raises urinary citrate, means to increase the solubility of tricalcium dicitrate were sought. Two successful approaches were discussed in these prior patent
20 applications.

First, it was found that solid preparations of calcium citrate made with an excess of citrate (calcium/citrate molar ratio of less than 1.5 where a
25 value of 1.5 represents the ratio for tricalcium dicitrate) had greater aqueous solubility. Thus, in a synthetic solution which mimicked gastric juice (pH 3, 37°C), citrate-enriched calcium citrate (with calcium/citrate molar ratio of 0.67) in a solid form was
30 8.85 times more soluble than tricalcium dicitrate. This calcium-enriched calcium citrate was also found to be more absorbable from the intestinal tract. In three normal subjects, the rise in urinary calcium after taking this modified solid form of calcium citrate was 24% greater

than following ingestion of an equivalent amount of tricalcium dicitrate.

Second, a more soluble form of calcium citrate could 5 be prepared by pre-mixing fixed amounts of calcium hydroxide and citric acid sufficient to achieve a desired molar ratio of calcium and citrate. When added to water, the mixture readily dissolved, yielding soluble calcium and citrate without elaboration of carbon dioxide. This 10 "pre-mix" of calcium hydroxide and citric acid was much more suitable in preparing liquid calcium preparations, than pre-formed citrate-enriched calcium citrate which took longer to dissolve.

15 In this continuation-in-part, additional data supporting utility of a pre-mix of calcium compound and citric acid in preparing a liquid preparation of calcium are presented. A readily soluble, powdered preparation of citric acid and a calcium compound such as calcium 20 hydroxide, containing a desired amount of calcium, may be dissolved in an aqueous solvent such as water, fruit juice or soft drink prior to ingestion. Different mixtures with varying relative amounts of calcium compound and citric acid were tested in order to determine which demonstrated 25 optimum solubility, calcium bioavailability and citraturic action. Such a preparation should be particularly useful in the correction of hypocalcemia in patients with hypoparathyroidism, in the prevention of bone loss in postmenopausal women, in the control of phosphate 30 retention in patients with end-stage renal failure and in the treatment of essential hypertension.

Liquid dietary calcium supplementation, useful in the prevention or treatment of hypoparathyroidism, 35 postmenopausal osteoporosis, phosphate retention of

chronic renal failure and essential hypertension, is accomplished by a readily soluble pre-mix of citric acid and a calcium compound, preferably calcium hydroxide.

5 From the aforementioned actions of liquid calcium supplementation from readily solubilized premixes of calcium compound and citric acid, it should be apparent that these readily soluble mixtures should be more effective than tricalcium dicitrato (solid), or certainly 10 calcium carbonate, in the management of various clinical disorders described earlier herein.

Calcium carbonate is the most widely used calcium supplement. There is theoretical basis for the assertion 15 that calcium citrate may be more optimal for the treatment of hypoparathyroidism. First, calcium is more absorbable from calcium citrate than from calcium carbonate. While calcium carbonate generally requires adequate gastric acid secretion for dissolution and absorption, the absorption 20 of calcium citrate is less dependent on acid secretion especially in its modified (readily soluble pre-mix) form. The difference in calcium absorbability between the two salts may be more marked in hypoparathyroidism, because 25 gastric acid secretion may be impaired owing to hypocalcemia. The improved calcium bioavailability of calcium citrate may reduce the requirement for vitamin D substances.

Second, calcium citrate therapy should augment 30 citrate excretion, especially when given in the citrate-rich form. There should be a reduced propensity for the crystallization of stone-forming calcium salts in urine due to the inhibitor activity of citrate. This action should help reduce the risk for stone formation which may 35 sometimes complicate this condition.

Third, calcium citrate is capable of binding dietary phosphate in the intestinal lumen. This binding capacity should be greater for mixtures of calcium hydroxide and citric acid than by calcium carbonate or solid tricalcium dicitrate because of the greater or more rapid solubility of pre-mixes and availability of calcium. Thus, there should be a better control of hyperphosphatemia.

In recent reports, calcium carbonate has been shown to be ineffective in preventing vertebral bone loss in postmenopausal women (Christiansen et al., J. Bone Min. Res. 166A, 1986). Prior studies of the present inventors indicated that tricalcium dicitrate may be potentially more effective than calcium carbonate in preventing bone loss. Our prior patent application (S.N. 807,530) presented preliminary data showing that calcium citrate may avert further bone loss. This conclusion was derived from findings that calcium citrate (a) provides a modest but definite alkali load which may exert a protective effect against bone loss, (b) confers greater calcium bioavailability, and (c) may be associated with a reduced risk for the crystallization of stone-forming calcium salts because of citraturic response. Liquid calcium supplementation in the form of mixtures of calcium hydroxide and citric acid should be more effective than tricalcium dicitrate because of its greater solubility, bioavailability, provision of alkali load and citraturic action.

There is a sound theoretical basis for the assertion that tricalcium dicitrate therapy should ameliorate complications of chronic renal failure.

First, calcium citrate should prevent phosphate retention by binding phosphate in the intestinal tract.

High doses of another calcium salt (calcium carbonate, 3-20 g calcium/day) has been shown to prevent the absorption of ingested phosphate (Clarkson et al., Clin. Sci., Sol. 30, pp 524-438, 1966). Calcium citrate may be more

5 effective than calcium carbonate in binding phosphate in the intestinal tract and in averting phosphate retention. Before calcium can bind phosphate in the gut, calcium must be dissociated from its associated anion. Calcium citrate has a greater aqueous solubility than calcium carbonate.

10 This fact partly accounts for the higher calcium absorbability (bioavailability) from calcium citrate. Thus, more free calcium should be available from calcium citrate than from calcium carbonate to complex phosphate in the gut. This conclusion is supported by the study of

15 McDonald et al., (Clin. Sci., Vo. 26, pp 27-39, 1964), who found that a "modest" dose of calcium citrate (2 g calcium/day) was effective in restoring normal serum phosphate concentration in patients with renal failure. Our own preliminary data has shown that a satisfactory

20 control of hyperphosphatemia could be achieved in the majority of patients with tricalcium dicitrate at a dose of 1.5-2.75 g calcium/day. Moreover, serum aluminum concentration declined from 127 ng/ml (before treatment) to 79 ng/ml after 8 weeks of treatment ($p<0.05$).

25

Second, calcium citrate supplementation may provide sufficient calcium for absorption to avert malabsorption of calcium in patients with end stage renal disease. Calcium citrate may be more effective in this regard than

30 calcium carbonate, the most widely-used calcium salt. Third, calcium citrate supplementation might obviate the need for the use of aluminum-containing antacids to bind phosphate, thus reducing aluminum load. The decline in serum aluminum concentration was previously enumerated.

Finally, calcium citrate may ameliorate metabolic acidosis since it provides an alkali load.

The above expectations for tricalcium dicitrate should be even more applicable for the liquid calcium supplementation with mixtures of calcium hydroxide and citric acid. Because of its rapid solubility, such pre-mixes should be more effective in binding phosphate and controlling hyperphosphatemia. They should be more effective in averting secondary hyperparathyroidism because of its greater calcium absorption. There should be a better control of metabolic acidosis since higher alkali load (citrate) would be delivered.

The present invention derives in part from observations concerning the effects of calcium carbonate, tricalcium dicitrate (solid) and placebo in essential hypertension. Neither calcium carbonate nor tricalcium dicitrate (800 mg calcium/day) was effective in lowering blood pressure. It is expected that liquid calcium supplementation in the form of mixtures of calcium hydroxide and citric acid should show hypotensive action, because of its greater calcium absorbability and alkali load.

Following is a summary of studies done with pre-mixes of calcium hydroxide and citric acid, showing superior solubility and absorbability.

Several mixtures of calcium compound and citric acid were tested. Their calcium/citrate molar ratio ranged from 1.5 to 0.67. Solubility (defined as the amount of total calcium remaining in solution) was tested for these mixtures containing 500 mg calcium in 300 ml of water. The solubility was dependent on pH, time of incubation and

the calcium/citrate molar ratio. All mixtures readily dissolved in water. All mixtures dissolved rapidly and remained in solution for at least 1 hour at a wide pH range (2-7). With a longer duration of incubation as well as at higher pHs, calcium precipitation occurred (as calcium citrate), leaving less calcium in solution. After 24 hours of incubation the final solubility approximated that found when corresponding solid form of calcium citrate and citric acid were used to formulate the same 10 calcium/citrate compositions. The period required for the precipitation of calcium citrate after initial dissolution was more prolonged for citrate-rich mixtures with lower calcium/citrate ratios. The final solubility was higher for mixtures with lower calcium/citrate ratios.

15

The absorption of calcium from the intestinal tract, tested in normal subjects, was greater from liquid calcium formulations prepared from mixtures of calcium compound and citric acid than from a solid preparation of preformed 20 tricalcium dicitrate. The absorption of calcium from the mixture with a calcium/citrate molar ratio of 1.5 was 27-63% greater than that from the preformed solid preparation with same molar ratio (tricalcium dicitrate). The highest bioavailability among various preparations tested was 25 obtained with the pre-mix of calcium compound and citric acid with a calcium/citrate molar ratio of 1.25.

Ingestion of dissolved mixtures of calcium hydroxide and citric acid, especially those containing an excess of 30 citric acid, caused a more prominent rise in urinary citrate (inhibitor of stone formation), than ingestion of a comparable amount (in terms of calcium content) of solid tricalcium dicitrate.

Thus, mixtures of citric acid and a calcium compound such as calcium hydroxide represented effective means of providing liquid calcium supplementation. They could be dissolved rapidly in an aqueous liquid or a soft drink 5 before ingestion. The pre-mix preparation with a calcium/citrate molar ratio of 1.25 was particularly suitable because of desired citrate content (60 meq/day assuming calcium intake of 1 g/day), adequate solubility and optimum calcium bioavailability. Other mixtures with 10 different molar ratios may be useful under special circumstances. Owing to these properties, liquid calcium supplementation provided by mixtures of a calcium compound such as calcium hydroxide and citric acid may be more useful than tablet preparations of tricalcium dicitrate 15 for raising serum calcium concentration in hypoparathyroidism, preventing bone loss in early postmenopausal women, controlling hyperphosphatemia in renal osteodystrophy and in lowering blood pressure in calcium-sensitive essential hypertension. Moreover, it is 20 expected that such liquid calcium supplementation would be associated with a further reduction in the risk for stone formation, due to a more prominent citraturic action.

The present invention relates to presented evidence 25 that mixtures of citric acid and a calcium compound such as calcium hydroxide as a form of liquid calcium supplementation are more optimal than tricalcium dicitrate provided, for example, in a tablet form. Although calcium hydroxide is a preferred calcium compound, it is 30 understood that calcium oxide and calcium carbonate may be equally useful in the practice of the present invention. A more detailed description follows.

First, mixtures of calcium hydroxide and citric acid 35 were found to be much more rapidly soluble than tricalcium

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dicitrate. Solubility was determined for 500 mg calcium (representing a typical prescribed dose) in 300 ml of water (representing gastric juice volume after ingestion of water with calcium supplement) at pH 2-7. The mixtures 5 of calcium hydroxide and citric acid, ranging in calcium/citrate molar ratio of 0.67 to 1.5, rapidly and completely dissolved in water at all pHs. Subsequently, calcium citrate precipitated out of solution. The time required for initiation of precipitation depends on the 10 citrate content and on pH. Thus, the precipitation took place within one hour of dissolution in the case of the mixture with a calcium/citrate molar ratio of 1.5 (representing the molar ratio for tricalcium dicitrate). However, for the citrate-enriched mixture with a 15 calcium/citrate molar ratio of 0.67, more than 2 hours were required to initiate calcium citrate precipitation. Moreover, for all mixtures, precipitation occurred at high pHs but not at low pHs. The total amount of calcium citrate precipitation was greatest for the mixture with 20 highest calcium/citrate ratio (1.5), and smallest for the citrate-enriched mixture with calcium/citrate molar ratio of 0.67. When the precipitation was complete, the solubility of calcium citrate approximated that of the corresponding preformed calcium citrate (with same 25 calcium/citrate ratio).

In contrast, the preformed solid preparation of tricalcium dicitrate underwent only gradual dissolution, especially at higher pHs. The preformed solid 30 preparations of calcium citrate with an excess of citrate (to yield calcium/citrate molar ratio of less than 1.5) had enhanced solubility. However, for these preformed solid preparations, the rate of dissolution was too slow to be useful in making liquid calcium supplements.

The final solubility of calcium citrate was the same for the precipitated material as was for the preformed compound. However, mixtures of calcium hydroxide and citric acid initially dissolved rapidly and gradually 5 allowed precipitation of calcium citrate. In contrast, preformed solid preparations of calcium citrate gradually dissolved, yielding soluble calcium and citrate. Thus, the pre-mixes of calcium hydroxide and citric acid served as convenient means of rapidly providing calcium (and 10 citrate) in a liquid form. By adding an excess of citric acid, the precipitation of calcium citrate could be delayed, and the preparation could be kept in a soluble form longer.

15 Second, calcium bioavailability (absorbability from intestines upon oral ingestion) was greater from liquid formulations prepared from mixtures of calcium hydroxide and citric acid than from solid tricalcium dicitrate. Ten normal subjects underwent indirect measures of intestinal 20 calcium absorption four times, after receiving orally 500 mg calcium as tricalcium dicitrate (solid form), and as pre-mixes of calcium hydroxide and citric acid with molar calcium/citrate ratios of 1.5, 1.25 and 0.67 (in liquid form). The pre-mixes yielded greater absorbability of 25 calcium than tricalcium dicitrate. The increment in urinary calcium during the second two hours after taking liquid calcium supplements was 18-74% greater than that following ingestion of solid tricalcium dicitrate, with the highest value obtained for the pre-mix with 30 calcium/citrate molar ratio of 1.25. The calcium absorption was also measured more directly from the recovery of radiocalcium after taking labeled calcium preparations in 6 normal subjects. The intestinal calcium absorption was greater from liquid preparations made from 35 mixtures of calcium hydroxide and citric acid than from

the solid preparation of tricalcium dicitrate, with the highest value being obtained for the pre-mix with a calcium/citrate molar ratio of 1.25 (70% higher).

5 Third, the liquid calcium supplementation in the form of pre-mixes of calcium hydroxide and citric acid should be more efficient than as a solid or tablet preparation (tricalcium dicitrate) in binding phosphate in the intestinal tract. The binding of phosphate in the diet 10 more readily occurs with calcium in a soluble state rather than in a solid or precipitated form. As previously described, calcium and citrate may be kept in a soluble form metastably beyond the theoretical and actual final solubility by using readily soluble mixtures of calcium 15 citrate and citric acid.

Fourth, liquid calcium supplementation in the form of mixtures of calcium hydroxide and citric acid should provide a greater alkali load and citraturic response than 20 the solid preparation of tricalcium dicitrate. Since these mixtures yield greater amounts of citrate in a soluble form, more citrate should be absorbed to provide an alkali load and to raise urinary citrate. Thus, urinary citrate rose from 107 mg/4 hours without calcium 25 supplementation, to 137 mg/4 hours following ingestion of 500 mg calcium as pre-mix of calcium hydroxide and citric acid with a calcium/citrate molar ratio of 1.25, and to 174 mg/4 hours after taking the pre-mix with calcium/citrate molar ratio of 1.5. The citraturic 30 response should reduce the risk for the crystallization of stone-forming calcium salts (Harvey, Zobitz and Pak, J. Clin. Endo. Metab. Vol. 62, pp 1223-1225, 1985), albeit it may not totally eliminate the risk in some instances. The alkali load provided may also be beneficial for bone. In 35 16 women with nephrolithiasis (due to causes other than

absorptive hypercalciuria) studied, alkali load with potassium citrate therapy caused a stability of bone density in the distal third of the radius. The fractional change in bone density was -0.007 at 1 year, -0.005 at 2 years, -0.002 at 3 years and +0.008 at 4 years to avoid 5 impeding calcium absorption. Fifth, the ratio of citrate to phosphorous (primary as phosphate) is preferably above about 0.5, most preferably above about 5.6.

10 The following examples are presented to describe preferred embodiments and utilities of the present invention and are not meant to limit the present invention unless otherwise stated in the claims appended hereto.

15

EXAMPLE 1

Formulation of Pre-Mixes of Calcium Hydroxide and Citric Acid

20

Two formulations of the pre-mix with a calcium/citrate molar ratio of 1.25 were made in order to provide orange and lemon-lime flavor preparations.

25

The orange flavored preparation (each 234.2 g) contained 153.6 g citric acid, 74.0 g Ca(OH)_2 , 2.4 g orange flavoring, 4.0 g aspartame, 150 mg vitamin B₂, and 22 mg of Red No. 40-89%. Each 2.927 g of this material, which could be placed in an individual sachet or scoop, 30 contained 500 mg of elemental calcium.

The lemon-lime flavored preparation (each 232.3g) contained 153.6 g citric acid, 74.0 g Ca(OH)_2 , 1.7 g lemon-lime flavoring, 2.85 g aspartame, and 115 mg of

vitamine B_2 . Each 2.903 g of this material provided 500 mg of elemental calcium.

When 500 mg calcium amounts of above materials were 5 suspended in 300 ml of water, they dissolved very rapidly and produced a well-tolerated drink of satisfactory flavor.

In order to prevent clumping of powdered mixtures, 10 Cabosil (fumed silica NF) may be added.

EXAMPLE 2

15 Solubility of Mixtures of Calcium Hydroxide and Citric Acid with a Calcium Citrate Molar Ratio of 1.25

The aqueous solubility of a mixture of calcium hydroxide and citric acid with a calcium/citrate molar ratio of 1.25 was determined as follows. A sufficient amount of the mixture containing 500 mg of elemental calcium was suspended in 300 ml of water kept at 37°C and at various pHs (2-7) while the pH was maintained at the predetermined level. After 1, 2 and 24 hours of 20 incubation, the filtrate was analyzed for calcium. The amount of calcium recovered in the filtrate represented 25 solubility, where 100% recovery indicated complete solubility.

30 The pre-mix dissolved in water very rapidly (within 2 minutes). It remained in solution after 1 hour of incubation (Table 1). After 2 hours of incubation, crystallization of calcium citrate occurred at pH greater than 4.5, indicated by an appearance of visible 35 precipitate and a decline in calcium recovery. Below pH

4.5, the pre-mix was completely soluble. After 24 hours of incubation, precipitation was noticeable at pH greater than 3.5. The filtrate concentration of calcium was much lower than at an earlier period of incubation (2 hours).

5 The curve representing the solubility of precipitated calcium citrate from the dissolved pre-mix was indistinguishable from that of pre-formed calcium citrate (solid) of identical calcium/citrate ratio. The results suggested that at steady state conditions (24 hours of

10 incubation), the final crystalline material (and its solubility) was the same whether it was obtained from dissolution of the preformed calcium citrate or from precipitation from dissolved pre-mix of calcium hydroxide and citric acid. The advantage of the pre-mix is that

15 this device allows for a preparation of a liquid formulation of calcium citrate much more rapidly and at a higher calcium concentration than might be possible from preformed solid calcium citrate.

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Table 1.

5 Solubility of Pre-mix of Calcium Hydroxide and Citric Acid with Calcium/Citrate Molar Ratio of 1.25

Percent of Calcium Recovered in the Filtrate				
10	pH	1 hr	2 hr	24 hr
	2.0	99.3	99.6	99.0
	2.5	99.3	99.0	97.8
	3.0	98.1	98.6	94.6
	3.5	97.8	98.4	95.9
15	4.0	97.8	97.4	35.6
	4.5	97.5	95.4	17.2
	5.0	91.2	73.9	15.0
	6.0	95.7	63.8	19.1
	7.0	95.4	58.9	22.0

20

EXAMPLE 3

25 Relative solubility of Different Pre-Mixes of Calcium Hydroxide and Citric Acid

The solubility of various pre-mixes (calcium/citrate molar ratio of 1.5, 1.25 and 0.67) was determined as described in Example 2, and compared with that of tricalcium dicitrate (also 500 mg calcium per 300 ml). After 2 hours of incubation, tricalcium dicitrate displayed expected solubility, with high dissolution at low pHs and reduced/limited dissolution at high pHs (Table 2). The pre-mix of calcium hydroxide and citric acid with

an identical calcium/citrate molar ratio of 1.5 had a much higher solubility. Both preparations were completely soluble or nearly so at a pH of 2.0 and 2.5. At higher pHs, the pre-mix gave a much greater calcium recovery at 5 this early period of incubation.

The pre-mixes with an excess of citric acid (calcium/citrate molar ratios of 1.25 and 0.67) had an even greater solubility. The preparation with the highest 10 solubility was the pre-mix with calcium/citrate molar ratio of 0.67. It was completely soluble even at high pHs.

Thus, pre-mixes with an excess of citric acid (for 15 example, calcium/citrate molar ratio of 1.25 and 0.67) allowed more calcium to remain in solution even in the neutral pH of the intestinal juice (where calcium absorption takes place), than the pre-mix with the calcium/citrate ratio of tricalcium dicitrate, i.e.-1.5.

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TABLE 2

5

Solubility of Different Pre-Mixes
After 2 Hours of Incubation

		Percent of Calcium Recovered in the Filtrate			
10	pH	Pre-Mix (1.5)	Pre-Mix (1.25)	Pre-Mix (0.67)	Tricalcium Dicitrate
15	2.0	99.6	99.6	98.6	95.1
	2.5	99.5	99.0	99.7	95.0
	3.0	100.0	98.6	99.2	83.6
	3.5	99.5	98.4	99.4	61.3
	4.0	99.1	97.4	99.2	39.9
	4.5	--	95.4	91.7	25.3
	5.0	98.7	73.9	52.1	16.9
20	6.0	99.2	63.8	37.6	14.9
	7.0	96.3	58.7	38.8	14.3

Numbers below Pre-mix in parentheses indicate the calcium/citrate molar ratio in this and subsequent tables.

25

EXAMPLE 4

30 Absorption of Calcium from Different Pre-Mixes
Assessed by an Indirect Method of Oral Calcium Loading

Calcium absorption was measured indirectly in 10 normal subjects from the rise in their urinary calcium after ingestion of 500 mg calcium as a liquid formulation 35 of various pre-mixes or as a solid preparation of

tricalcium dicitrate. The increment in urinary calcium during the second two hours following oral calcium load was substantially higher after taking dissolved pre-mixes than after ingestion of solid tricalcium dicitrate (Table 5 3). This indirect measure of calcium absorption was greatest for the pre-mix with a calcium/citrate molar ratio of 1.25 than for other pre-mixes.

10 Thus, calcium was more bioavailable from liquid preparations of the pre-mixes than from solid tricalcium dicitrate.

TABLE 3

15

Indirect Measure of Calcium Absorption from Pre-Mixes

	Calcium Preparation	Increment in Urinary Calcium (mg calcium/100 ml glomerular filtrate)
20	Tricalcium dicitrate (1.5)	0.087 \pm 0.087
25	Pre-mixes (1.5)	0.142 \pm 0.061**
	(1.25)	0.151 \pm 0.061**
30	(0.67)	0.103 \pm 0.059

35 Values are presented as mean \pm SD. Significant difference from tricalcium dicitrate is shown by ** for $p<0.01$.

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EXAMPLE 5

Calcium Absorption from Pre-Mixes
Using a More Direct Method

5

In 6 normal subjects, intestinal calcium absorption was indirectly measured from the fecal recovery of radioactive calcium after giving by mouth liquid preparations of various pre-mixes or tricalcium dicitrate (solid preparation) pre-labeled with radiocalcium. The calcium absorption from pre-mixes was higher than from tricalcium dicitrate (Table 4). The highest absorption was obtained with the mixture of calcium hydroxide and citric acid with a calcium/citrate molar ratio of 1.25.

15

Table 4

Radiocalcium Absorption from Pre-Mixes

20

	Calcium Preparation	Calcium Absorption (%)
	Tricalcium dicitrate (1.5)	19.1±6.9
25	Pre-mix	
	(1.5)	24.3±10.2
30	(1.25)	32.5±5.3*
	(0.67)	23.9±13.5

35 Values are presented as mean \pm SD. Significant difference from tricalcium dicitrate is shown by * for $p < 0.05$.

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EXAMPLE 6

Effect of Pre-Mix Administration on Urinary Citrate

5 Following oral administration of 500 mg calcium as various pre-mixes (in a liquid form) or as tricalcium dicitrate (solid), urinary citrate was measured over 4 hours in 10 normal subjects (Table 5). As compared to the control value obtained without taking any calcium, urinary 10 citrate was greater after receiving liquid calcium supplements from pre-mix with calcium/citrate molar ratio of 1.25 and 0.67 (citrate-rich preparations).

15

Table 5

Urinary Citrate Following Oral Administration of Pre-Mixes

20

	Calcium Preparation	Urinary Citrate (mg/4 hour)
	Tricalcium dicitrate (1.5)	120 \pm 33
25	Pre-mix	
	(1.5)	118 \pm 33
30	(1.25)	137 \pm 50
	(0.67)	174 \pm 35+
35	Control	120 \pm 30

Values are presented as mean \pm SD. Significant difference from the control (without calcium supplementation) is shown by + for $p < 0.001$.

40

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EXAMPLE 7

Summary of Properties of Various Calcium Preparations

5 The mixture of calcium hydroxide and citric acid with a calcium/citrate molar ratio of 0.67 (citrate-rich) was most soluble, and had the greatest citrate content and citraturic action (Table 6). However, it had the lowest calcium bioavailability among the pre-mixes. The pre-mix 10 with a calcium/citrate molar ratio of 1.25 had the highest calcium bioavailability, and had adequate solubility, citrate content and citraturic action. Assuming a recommended calcium intake of 1 g/day, the amount of citrate contained in this pre-mix was 60 meq/day, a safe 15 level.

These varying properties might be utilized to special advantage under different clinical conditions, to suit particular needs of those conditions.

20

Table 6

Order of Efficiency of Different Calcium Preparations

25

		Pre-Mixes (1.5)	Pre-Mixes (1.25)	Tricalcium (0.67)	Dicitrate
30	Solubility	3	2	1	4
	Ca bioavailability	2	1	3	4
	Citraturic action	3	2	1	3
	Citrate content	3	2	1	3

35

EXAMPLE 8Solubility of Ca(OH)_2 and CaCO_3 in Orange Juice

5 Since orange juice is rich in citric acid, addition of calcium hydroxide or calcium carbonate results in the formation of calcium citrate. The following general stoichiometric reaction formulas indicate appropriate reactions.

10



15

Solubility of calcium hydroxide was determined in Minute Maid orange juice (concentrate diluted 1:3 with distilled water) at 6°C (refrigerated). This "diluted" juice (hereafter called simply orange juice) contained 45 mmoles of total citrate/liter; pH was 3.91. Increasing amounts of calcium hydroxide were added to 180 ml (6 oz) of orange juice, and stirred for 30 minutes. The filtrate of the stirred mixture was assayed for pH and calcium content (Table 7).

Table 7

Solubility of Calcium Hydroxide in Orange Juice

5

	<u>Sample</u>	<u>Amount of Ca added as Ca(OH)₂ (mg Ca)</u>	<u>Final pH</u>	<u>Filtrate Ca mg/180 ml</u>
10	1	100	4.15	106
	2	200	4.44	204
	3	300	4.83	305
	4	400	7.44	401
15	5	500	9.16	418

Calcium hydroxide readily dissolved (within 5 minutes) in samples 1 and 2. It dissolved more slowly (20 minutes) in sample 3. Samples 1-3 retained the original orange juice color. The final pH was less than 4.9 and final filtrate calcium closely approximated the amount added. However, in samples 4 and 5, final pH was much higher and there was grayish discoloration. Incomplete dissolution of calcium hydroxide was confirmed by the lower final filtrate concentration of calcium (compared to amount added) in Sample 5.

The results suggested that there is sufficient amount of free citric acid in orange juice to convert up to 300 mg calcium as calcium hydroxide/180 ml into soluble calcium citrate.

Similar results were obtained when calcium carbonate was added to orange juice. For example, when 300 mg calcium as calcium carbonate was added to 180 ml of Minute Maid orange juice (refrigerated), it dissolved rapidly (within 5 minutes). However, foam developed due to the elaboration of carbon dioxide. A mixture of calcium carbonate and calcium hydroxide (100 mg Ca as calcium carbonate and 200 mg calcium as calcium hydroxide) was added to 180 ml of orange juice. Rapid dissolution (within 5 minutes) again took place. There was less foam.

Thus, addition of calcium carbonate either alone or with calcium hydroxide provides rapid dissolution in orange juice. Unfortunately, the development of foam may limit the usefulness of calcium carbonate. Dissolution of calcium carbonate and citric acid in aqueous solutions or juices other than those as prone to foaming as orange juice is likely to be feasible to form a desired calcium compound/citric acid mixture analogously useful to the calcium hydroxide/citric acid combinations described earlier herein.

EXAMPLE 9

25

Effects of Phosphate and Citrate Upon Calcium Absorption

An important aspect of the present invention is illustrated by the effects of phosphate with or without citrate upon net calcium absorption by individuals ingesting a calcium-containing mixture. Commercially available carbonated soft drinks having different levels of phosphate were obtained. Calcium hydroxide or calcium hydroxide, phosphate as phosphoric acid and citric acid were dissolved in the soft drinks (pH 2-5) to result in

preparations A-D shown in Table 8. The phosphate content was measured by a standard phosphate assay and the content of elemental phosphorous calculated. Each mg of phosphorous was equal to about three mg of phosphate $5 (PO_4)$.

Table 8

10 Calcium, Citrate and Phosphorous Content of Liquid Preparations

		PREPARATION			
15		A	B	C	D
	Volume, ml	354	354	354	354
20	Ca, mg	100	100	100	100
	P, mg	114	114	51	0
	Citrate, mg	0	64	284	403
25	Ca/citrate, molar	0	7.14	1.67	1.18
	mg citrate/mg phosphorous	0	0.56	5.57	1.18

30 All four preparations contained the same amount of calcium (100 mg/354 ml). The preparation A contained phosphate but was devoid of citrate, whereas the preparation D contained adequate amount of citrate but no phosphate. Preparations B and C were intermediate. The 35 Ca/citrate molar ration of solution D approximated that of the most preferred embodiment of the present invention. Preparations B and C represented citrate-deficient solutions with a high Ca/citrate molar ration.

In 6 normal subjects, intestinal calcium absorption was determined from above preparations, from the fecal recovery of radioactivity after oral administration of preparations labeled with ^{47}Ca . The procedure is shown in

5 Example 5.

Preparations A-D were orally administered and subsequent fecal calcium content measured as described in Example 5. The results in terms of the fraction of 10 administered calcium absorbed are shown in Table 9.

Table 9

15 Calcium Preparation and Calcium Absorption

	PREPARATION	FRACTIONAL CA' ABSORPTION
20	A	0.309 \pm 0.081 SD
	B	0.340 \pm 0.125
	C	0.369 \pm 0.146
25	D	0.405 \pm 0.053

The calcium absorption was highest from preparation D which contained an excess of citrate without phosphate and 30 was lowest for preparation A which had phosphate but no citrate.

As the data of Table 9 indicates, citrate but not phosphate increases the absorption of calcium. The 35 mixture or liquid of the present invention preferably has a mg P/mg citrate ratio of less than about 1.5 to improve calcium absorption.

* * * * *

Changes may be made in the compounds and procedures
5 described herein without departing from the concept and
scope of the invention as defined in the following claims.

CLAIMS:

1. A composition of matter consisting essentially of
5 citric acid and one or more calcium compounds selected
from the group consisting of calcium hydroxide, calcium
carbonate and calcium oxide.
- 10 2. A composition of matter comprising citric acid and
one or more calcium compounds selected from the group
consisting of calcium hydroxide, calcium carbonate and
calcium oxide in a substantially dry mixture.
- 15 3. A composition of matter consisting essentially of
calcium hydroxide and citric acid in a calcium
hydroxide/citric acid molar ratio between about 0.6 and
about 3.0.
- 20 4. A composition of matter for dissolution in water to
form a liquid dietary calcium supplement comprising
soluble calcium citrate, the composition of matter being
25 substantially dry and consisting essentially of citric
acid and a calcium compound selected from the group
consisting of calcium hydroxide, calcium carbonate and
calcium oxide, the composition of matter being further
characterized in that the calcium compound and citric acid
30 are in a calcium compound/citric acid molar ratio between
about 0.6 and about 3.0.

5. The composition of matter of claim 1, 2, 3 or 4 defined further as comprising one or more of a flavorant, lubricant, sweetener or colorant.

5

6. The composition of matter of claim 1, 2, 3 or 4 defined further as having a calcium compound/citric acid or calcium hydroxide/citric acid molar ratio of about 1.25.

10

7. The composition of matter of claim 1, 2, 3 or 4 defined further as having a phosphorous/citrate weight ratio of less than about 1.5.

15

8. A method for preparing a mixture soluble in an aqueous solvent to form a potable liquid consisting essentially of calcium citrate, the method comprising: 20 mixing calcium hydroxide and citric acid in a calcium hydroxide/citric acid molar ratio of between about 0.6 and about 3.0.

25 9. A method for preparing a potable liquid consisting essentially of calcium citrate and citric acid, the method comprising:

30 preparing a mixture comprising calcium hydroxide and citric acid in a calcium hydroxide/citric acid molar ratio of between about 0.60 and about 3.0; and

35 dissolving a quantity of said mixture in an amount of aqueous solvent.

10. A potable liquid suitable for dietary supplementation of calcium without substantial risk of calcium renal stone facilitation or enhancement the preparation consisting essentially of:

5

a calcium compound selected from the group consisting of calcium hydroxide, calcium oxide and calcium carbonate;

10 citric acid; and

water.

15 11. The potable liquid of claim 10 defined further as having a pH between about 2 and about 7.

20 12. The potable liquid of claim 10 defined further as having a pH between about 3 and about 5.

25 13. The potable liquid of claim 10 defined further wherein the calcium compound and citric acid are in a calcium compound/citric acid molar ratio between about 0.6 and about 3.0.

30 14. The potable liquid of claim 10 defined further as comprising calcium in an concentration between about 500 mg/L and about 2000 mg/L.

35 15. The potable liquid of claim 10 wherein the calcium compound is defined further as being calcium hydroxide.

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16. The potable liquid of claim 10 defined further wherein the calcium compound and citric acid are in a calcium compound/citric acid molar ratio between about 0.6 and about 1.5.

5

17. The potable liquid of claim 10 defined further as having a phosphorous/citrate weight ratio of less than about 1.5.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 87/03066

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁴

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC⁴: A 23 L 2/38; A 61 K 31/19

II. FIELDS SEARCHED

Minimum Documentation Searched ⁷

Classification System	Classification Symbols
IPC ⁴	A 23 L

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched ⁸

III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	DE, B, 1915509 (N.V. ORGANON) 25 February 1971, see claims 1,4,5; example 1 --	1-4,8-16
X	EP, A, 0052677 (MONSANTO) 2 June 1982, see claim 1; page 59, line 16 - page 60, line 8 --	1,2,4,5, 10,13,14, 16
A	EP, A, 0117653 (PROCTER & GAMBLE) 5 September 1984, see claim 1; example 2 --	7,17
A	US, A, 2953459 (I.M. DILLER) 20 September 1960 -----	

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IV. CERTIFICATION

Date of the Actual Completion of the International Search

26th February 1988

Date of Mailing of this International Search Report

20.04.88

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

P.C.G. VAN DER PUTTEN

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.

US 8703066
SA 19824

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 11/04/88. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
DE-B- 1915509	25-02-71	NL-A-	7004089	29-09-70
		FR-A, B	2051492	09-04-71
		US-A-	3663271	16-05-72
		GB-A-	1300969	29-12-72
		CH-A-	535596	15-04-73
		BE-A-	748006	28-09-70
		SE-B-	373359	03-02-75
EP-A- 0052677	02-06-82	AT-B-	E11094	15-01-85
EP-A- 0117653	05-09-84	AU-A-	2393684	02-08-84
		JP-A-	59187768	24-10-84
		US-A-	4551342	05-11-85
		CA-A-	1214065	18-11-86
		AU-B-	559577	12-03-87
US-A- 2953459		None		

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